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IN THE CLAIMS: See Listing of Claims attached hereto which will replace all prior versions of claims in the application.

REMARKS

The Office requests a priority statement in the Specification. As we advised previously, this is not an application claiming foreign priority under 35 USC § 119, but rather a National Phase filing under 35 USC § 371. It is not, consequently, appropriate to make such notation at the beginning of the Specification. The applicant however, is required under MPEP Section 1893.03(a) to claim that the original submission is a "submission to enter the National stage under 35 USC § 371." This statement is included in our Form PCT/DO/EO/1390, with which the application was filed.

The Office maintains a requirement for a full translation of French Application, 98/03,814. The Applicants have noted the Office's non-statutory suggestion. The required English translation of International application number PCT/FR99/00703 was provided and acknowledged in the USPTO Form PCT/DO/EO/905 of November 6, 2000.

The applicants are requested to provide an abstract on a separate page. We reiterate our statement regarding the MPEP directions on such requirement. Under MPEP § 1893.03(e) the Office is to rely on the abstract which is printed on the cover of the PCT abstract. The Applicants point out that such an abstract, in English, is clearly present on the cover page of the instant application.

With regard to the Examiner's repeated objections as to form, the Applicants note that the MPEP guidelines are formulated to facilitate the rapid and uniform prosecution of applications. We suggest that the Examiner consult with his

supervising attorney before making formal objections which are without basis and delay the prosecution of this application.

The Office requires that the Applicants provide proper sequence notation and disclosure for every sequence disclosed in the Specification. The Office specifically notes the sequence at page 7, line 36 of the Specification. The sequence identifier, "residues 1 to 9 of SEQ ID No 2" has been appropriately incorporated in the replacement paragraph for page 7, lines 26-39 of the Specification with the accompanying Amendment to the Specification.

The Office action of June 17, 2003 is hereby acknowledged with appreciation. Claims 22-40 remain pending in the application. Claims 22-39 are rejected under 35 USC § 101 for being improper 'use' claims. Presently, Claims 23, 24, 26-32, 34-37 and 39 are amended to conform to U.S. 'method' claims, such claims having basis in the original European "Use" claims and such amendment being customary upon entry into U.S. National Phase prosecution. The instant invention is now drawn to a method of enhancing the immunity of a mammal, with respect to the particular antigen or hapten through, specifically, intranasal administration of a pharmaceutical preparation containing *Klebsiella pneumoniae* outer membrane type A protein having the sequence SEQ ID No. 2 combined with an antigen or hapten.

Claims 22-39 are rejected under 35 USC § 112, first and second paragraphs, for lack of enablement and indefiniteness, respectively. The Office concludes that the instant Specification is enabling for the use of rP40 protein of *Klebsiella pneumoniae;* however, it is the position of the Office that the specification does not provide enablement for use of other enterobacterium proteins and fragments that are claimed. Applicants have identified appropriate limitations upon review of the analysis by the Office. Claims 22, 23, 24, 35, 37 and 38 are presently amended to encompass the *K. pneumoniae* membrane protein OmpA of SEQ ID No. 2. Applicants submit that these amendments provide the requested definition.

Moving on to the prior art rejections, the Office rejects Claims 22-39 for anticipation under 35 USC § 102 (a) in view of Rauly, et al., (European Journal of Biochemistry, Vol. 255, pp. 446-454, July 1998). Applicants acknowledge Haeuw, et al., [the proper first author of this citation] (European Journal of Biochemistry, Vol. 255, pp. 446-454, July 1998) disclose that the *Klebsiella pneumoniae* P40 protein increased the level of antibodies against an associated antigen when administered subcutaneously. As it is not possible, nor is it the intent of the Applicants to patent such composition, but rather the method of using such composition, specifically through intranasal administration. Applicants have demonstrated that, in the absence of another adjuvant, intranasal administration of *K. pneumoniae* OmpA increases the level of antibodies directed against an associated antigen and that such antibodies are present in serum and in broncho-alveolar fluid. Applicants submit there is no anticipation of the performance of this protein to elicit this type of immune response when administered to a mammal intranasally.

Additionally, the Office rejects Claims 22-39 for anticipation under 35 USC § 102 (b) in view of the disclosure of Rauly, et al., (Research in Immunology, Vol. 149, No. 1, pp. 99, January 1998). It is the position of the Office that Rauly, et al. teach the claimed protein, and consequently, that the intended use of the instant protein does not impart patentability to the composition. Rauly, et al. disclose the use of *Klebsiella pneumoniae* OmpA protein for improving immunity of a mammal with respect to an antigen in the absense of any adjuvant. The instant invention is now drawn to a method of enhancing immunity, specifically, through intranasal administration, of a pharmaceutical composition comprising *Klebsiella pneumoniae* OmpA protein. Rauly, et al. provide little guidance as to the method used for *in vivo* immunizations. Consequently, there is no teaching that immunizations were, specifically, through an intranasal route. Immunity to an antigen can be generated by any of several routes of administration routine in the art, including subcutaneous,

intraperitoneal, intravenous routes. The route of administration impacts how quickly the immunogen is released into the lymphatics or circulation, such methods are chosen deliberately for the desired outcome. Applicants have demonstrated the intranasal administration of *K. pneumoniae* OmpA protein, P40 increases the level of antibodies directed against an associated antigen and that such antibodies are present in serum and in broncho-alveolar fluid. The reference does not disclose nor suggest the capacity of the instant invention to achieve a serum antibody response through intranasal immunization, or particularly, an antibody response in broncho-alveolar system. The presence of such antibodies in the broncho-alveolar system is desireable because these antibodies can protect a mammal against a potential infection directly at this level. The cited prior art neither disclose, nor suggest this surprising activity. Consequently, the rejection for anticipation is not supported by the art of record. In light of these remarks, reconsideration and withdrawal of the prior art rejection is respectfully solicited.

Moreover, and with respect to any potential conclusion by the Office that the prior art suggest the instant invention, the Applicants invite the Office to consider the disclosure of Erdile, et al., (Vaccine, Vol. 15, No. 9, pp.988-996, 1997) [cited in the International Search Report and made of record on PTO Form 892 of the instant action], in light of the presently amended Claims 22-39, drawn to intranasal administration *Klebsiella pneumoniae,* P40. This reference discloses an immunogenic composition comprising the outer surface protein A (OspA) lipoprotein of *B. bergdorferi* as a mucosal immunogen and adjuvant upon co-administration with antigen. Erdile, et al. clearly demonstrates that the lipidic constituent is absolutely required for obtaining an immune response by intranasal route (Results section, entitled, "The lipid moiety is required to induce and immune response by the i.n. route"). Applicants submit, consequently, it would not have been obvious for one skilled in the art at the time of the present invention to use a purified peptide, without

such lipid moiety, to increase the antibody response directed against an associated antigen when administered intranasally in a mammal.

Considering the above remarks, the Applicants submit that they have demonstrated the novelty of the instant invention, in that the intranasal administration of *K. pneumoniae* OmpA protein, P40, in the absence of another adjuvant, increases the level of antibodies directed against an associated antigen (such as G1' which is derived from the RSV protein G) and that such antibodies are present in serum and in broncho-alveolar fluid. The presence of such antibodies in the broncho-alveolar system is of great interest because these antibodies can protect a mammal against a potential infection directly at this level. None of the cited documents disclose nor suggest that *K. pneumoniae* P40 OmpA protein improves the immune response against and associated antigen when administered intranasally, particularly at the broncho-alveolar level. What is more, the applicants have referenced disclosure known to those skilled in the art that the instant method would not be expected to be successful.

* * * * *

Accordingly, entry of the present amendment, reconsideration of all grounds of objection and rejection, withdrawal thereof, and passage of this application to issue are all hereby respectfully solicited.

It should be apparent that the undersigned attorney has made an earnest effort to place this application into condition for immediate allowance. If he can be of assistance to the Examiner in the elimination of any possibly-outstanding insignificant impediment to an immediate allowance, the Examiner is respectfully invited to call him at his below-listed number for such purpose.

Allowance is solicited.

Respectfully submitted,

THE FIRM OF HUESCHEN AND SAGE

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Enclosure: Listing of Claims, Amendment to the Specification, Extension Fee (Three months) $950.00, and Postal Card Receipt

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Listing of Claims

PF 82 PCT SEQ

Claim 22. (currently amended): ~~Use of at least one fragment of a membrane protein for preparing a pharmaceutical composition intended to be administered nasally, selected from the group consisting of :~~
~~an enterobacterium membrane protein,~~
~~an enterobacterium membrane protein OmpA,~~
~~a Klebsiella membrane protein, and~~
~~a *Klebsiella pneumonia* membrane protein OmpA useful for~~ The method of improving immunity of a mammal with respect to an antigen or a hapten, through intranasal administration of a pharmaceutical composition comprising, the *Klebsiella pneumoniae* membrane protein OmpA having the sequence SEQ ID No. 2, combined with the antigen or the hapten.

Claim 23. (currently amended): [[Use]] The method of Claim 22 wherein the membrane protein ~~or its fragment~~ is obtained by a recombinant process.

Claim 24. (currently amended): [[Use]] The method of Claim 23 wherein the recombinant membrane protein ~~or its fragment~~ is renatured in the presence of a detergent selected from the group Zwittergent 3-14, Zwittergent 3-12, and octylglucopyranoside.

Claim 25. (canceled)

Claim 26. (currently amended): [[Use]] The method of claim 22 wherein the antigen or hapten are selected from the group consisting of proteins, peptides, polysaccharides, oligosaccharides and nucleic acids.

Claim 27. (currently amended): [[Use]] The method of Claim 26 wherein the antigen or hapten originate from a virus or a bacterium.

Claim 28. (currently amended): [[Use]] The method of Claim 27 wherein the antigen or hapten comprise at least one protein fragment of a microorganism responsible for pathologies of the airway.

Claim 29. (currently amended): [[Use]] The method of Claim 28 wherein the microorganism is selected from the group consisting of RSV, parainfluenza virus (PIV), influenza virus, hantavirus, streptococci, pneumococci and meningococci.

Claim 30. (currently amended): [[Use]] The method of Claim 26 wherein the antigen or hapten comprises at least one protein fragment of the human or bovine respiratory syncytial virus (RSV).

Claim 31. (currently amended): [[Use]] The method of Claim 30 wherein the antigen or hapten comprises at least one fragment of the G protein of the RSV.

Claim 32. (currently amended): [[Use]] The method of Claim 30 wherein the antigen or hapten comprises at least one of the sequences SEQ ID No. 3 through SEQ ID No.136.

Claim 33. (currently amended): [[Use]] The method of Claim 31 wherein the antigen or hapten comprises at least one of sequences SEQ ID No. 3 through SEQ ID No.136.

Claim 34. (currently amended): [[Use]] The method of Claim 22 wherein the membrane protein ~~or its fragment~~ is covalently coupled to the antigen or hapten.

Claim 35. (currently amended): [[Use]] The method of Claim 34 wherein one or more bonding elements is introduced into the membrane protein ~~or its fragment~~ and/or introduced into the antigen or hapten to facilitate the coupling, forming a hybrid protein.

Claim 36. (currently amended): [[Use]] The method of Claim 35 wherein the bonding element introduced is an amino acid.

Claim 37. (currently amended): [[Use]] The method of Claim 36 wherein the hybrid protein, obtained after coupling between the membrane protein ~~or its fragment~~ and the antigen or hapten, wherein the antigen or hapten is protein in nature, is prepared by genetic recombination.

Claim 38. (currently amended): [[Use]] The method of Claim 37 including a transformed host cell which is capable of expressing a hybrid protein containing said ~~fragment of~~ membrane protein coupled to said antigen or hapten.

Claim 39. (currently amended): [[Use]] The method of Claim [[38]] 22 which does not contain an adjuvant.

Claim 40. (withdrawn) A method of preparing a protein or one of its fragments by recombinant process wherein said protein or one of its fragments is, after extraction, renatured in the presence of a solution comprising a detergent chosen from Zwittergent 3-14, Zwittergent 3-12 and octyglucopyranoside, and wherein said recombinant protein is not interferon β.

Amendment to the Specification: PF82 PCT SEQ

Please replace the original paragraph on page 7, lines 26-39 with the following amended paragraph:

Example 1: Cloning of rP40

Cloning of the rP40 gene:

The gene encoding rP40 was obtained by amplification by PCR (Polymerase Chain Reaction) from the chromosomal DNA of the Klebsiella *pneumoniae* IP I145 strain (described in patent WO 96/14415). After identification by DNA sequencing, the fragment corresponding to rP40 is cloned into diverse expression vectors, in particular the one under the control of the trp operon promoter, upstream of 9 amino acid of the leader peptide (MKAIFVLNA), residues 1 to 9 of SEQ ID No 2. The peptide sequence of rP40 is represented in the sequence listing by the sequence SEQ ID No 1. In various *E. coli* K12 strains, the rP40 protein is produced in the form of inclusion